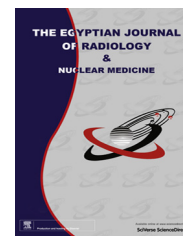




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ORIGINAL ARTICLE

Role of cerebral CTA screening on treatment planning and outcome in patients with left sided infective endocarditis



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KEYWORDS

Intracranial mycotic aneurysm (ICMA);
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Abstract Large number of infective endocarditis (IE) patients remain clinically silent till hemorrhagic events occur with very poor outcome. The aim of this work was to study the impact of detection of this silent group by cerebral CT angiography (CTA) – which is not a standard practice – on the treatment decisions and outcome in patients with left sided IE.

Patients and methods: From July 2007 to December 2012, 81 patients with left-sided IE (mean age was 30.43 ± 8.8 years. 49 males) had brain CTA within 1 week of admission. All patients with ICMA underwent four-vessel angiography. Treatment of intracranial mycotic aneurysms (ICMA) was done either by endovascular or surgery.

Results: Brain CTA revealed 51 patients with cerebral embolization. 26 patients had ICMA, 13 went for endovascular treatment 6 of them were clinically silent. 2 went for open surgery and 11 spontaneously thrombosed on treatment. The findings in brain CTA prompted changes in treatment decisions in 21 patients (25.6%). The mortality in ICMA patients was 19.2% which is significantly lower than most of the published literature.

Conclusion: Routine assessment of patients with left sided IE by cerebral CTA can change the treatment plans leading to significant reduction in mortality rate and improved outcome.

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1. Introduction

Despite the advances in diagnostic and therapeutic modalities, infective endocarditis (IE) remains a challenging disease with

high rates of mortality and morbidity (1). Infective endocarditis (IE) is a condition resulting from microbial infection of the endothelial lining of intracardiac structures and is highly fatal if untreated. Infection most commonly resides on one or more heart valve leaflets, but may involve mural endocardium, chordal structures, myocardium and pericardium (2).

The disease may also occur within septal defects or on congenitally malformed structures. Infections of the great vessels, arteriovenous shunts and of arterioarterial shunts (like patent

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ductus arteriosus) as well as infection related to coarctation of the aorta (2).

Clinically manifest neurological complications occur in 20–40% of IE patients and are mostly due to septic brain embolization and formation of intracranial mycotic aneurysm (ICMA) (2). Neurological complications in (IE) are strong predictors of mortality which is between 60% and 83% with ruptured (ICMA) (3–5). Most of the ICMA remain silent and rupture suddenly with catastrophic consequences (6,7).

Intracranial mycotic aneurysms (ICMA) are rare compared with berry aneurysms. They develop as a consequence of vessel wall necrosis due to showering of bacterial emboli into the circulation, their evolution is unpredictable even after the commencement of antibiotic therapy, they can regress, develop de novo, or rupture (5). Occlusion of the aneurysm has been recommended, either by surgery (8–10) or more recently, with endovascular means (11–14).

Sub-clinical infarcts, cerebral hemorrhage or rupture ICMA can complicate the course of treatment and alter treatment decisions, particularly in patients who require cardiac surgery and valve replacement. Despite the high incidence and the grave prognosis, routine screening for neurological complications is not a standard practice in (IE). The aim of this work was to detect the impact of early screening of these complications by cerebral CTA on the treatment decision and outcome in patients with (IE) affecting the left side of the heart.

2. Patients and methods

From July 2007 to December 2012 we prospectively recruited 81 consecutive patients with left-sided IE confirmed by Trans-thoracic or trans-esophageal echography and blood/serology cultures. The mean age was 30.43 ± 8.8 years. Forty-nine were males (60.5%). All patients performed cerebral CT angiography (CTA) within 7 days of admission regardless of the presence of manifest neurological complaint, for which informed consent was obtained. Patients were examined on a 64-MDCT scanner Toshiba Aquilion (Toshiba Medical Systems Europe B.V. Zoetermeer, The Netherlands). All examinations were reviewed and discussed by two neuro-radiologists who assessed the presence, number, location and size of ICMA as well as the associated findings e.g. strokes, vasospasm and occlusions.

Patients were classified as having clinical evidence of brain embolization (symptomatic) if they had either new onset of a persistent focal neurological deficit or a transient ischemic attack (TIA) defined as brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction (15).

We diagnosed aneurysms as mycotic in the setting of definite IE and had one of the following criteria:

- The presence of another intra- or extra-cranial mycotic aneurysm.
- Rupture of the aneurysm.
- Arterial occlusion or stenosis adjacent to the aneurysm.
- Cerebral infarction due to arterial occlusion at the level of the aneurysm (16).

Patients with ICMA by CTA performed digital subtraction angiogram and went for treatment if they had one of the following:

- ICMA diameter ≥ 5 mm.
- Evidence of leak around the ICMA.
- Location of the ICMA in the same territory of a symptomatic cerebral infarction.
- Increase in ICMA size on subsequent follow up studies.

Patients with ICMA < 5 mm were scheduled for follow up angiography after two weeks of proper antimicrobial therapy. If the ICMA regressed or remained stable, then patients were managed conservatively. When cardiac surgery was performed in patients with ICMA, it had to be either valve repair or replacement by biological valve. We decided to hold oral anti-coagulation in patients with ICMA and to postpone non-emergent cardiac surgery for 2 weeks in these patients even if asymptomatic. Cardiac surgery was also postponed for 2 weeks in patients with cerebral hemorrhage or large cerebral infarcts even if asymptomatic. We excluded patients who refused to sign the informed consent and patients who refused angiography. The local ethical committee approved the study protocol.

Thirteen patients in this study went for endovascular treatment. Technical details were discussed with the patient or relatives and an informed consent was obtained for the procedures. All endovascular treatment procedures were performed under general anesthesia. A guiding catheter 6-F was introduced till the upper cervical level with continuous flushing with normal saline. Intravenous heparin shots to obtain an activated partial thromboplastin time two to three times baseline were performed.

Distally located aneurysms ($n = 10$) were treated with endovascular parent artery occlusion (PAO) where selective occlusion of the aneurysmal sac with coils cannot be achieved. Usually adequate collateral circulation in young age group treated by PAO prevents infarction in the territory of the occluded vessel. If infarction occurs, the clinical consequences are going to be limited or clinically silent (17,18). Coiling was done for proximal aneurysms ($n = 3$).

For distal aneurysms a flow-guided microcatheter (Magic, Balt, France) or an over-the-wire microcatheter (Excel 10, Target Therapeutics) was used. The microcatheter was positioned as close as possible to the aneurysm to occlude the parent artery and the aneurysmal sac using cyanoacrylate (Histoacryl; B Braun, Melsungen, Germany) mixed with iodized oil (Lipiodol Ultra Fluide; Laboratoire Guerbet, Paris, France) in ratios varying from 1:1 to 1:3. In proximal aneurysms selective treatment by coiling was performed with a technique similar to that used in the treatment of berry aneurysms using Guglielmi detachable coils (Target Therapeutics).

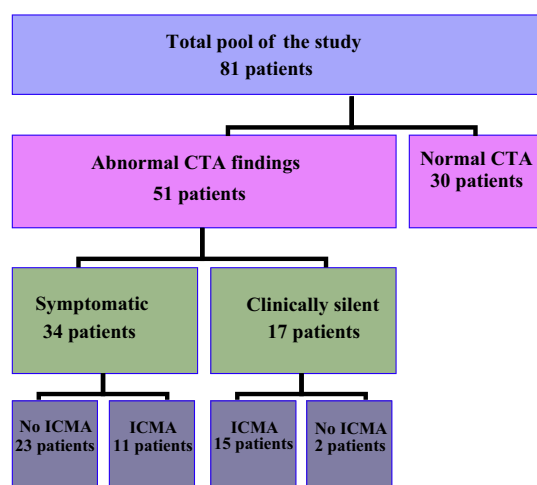
3. Results

The cerebral CTA findings, clinical features, and complications in our study group are demonstrated in Table 1 and Diagram 1.

Twenty-six patients had ICMA by CTA, 15 of them were clinically silent. Associated 3 extra-cranial mycotic aneurysms were found in two patients; one involving the right ICA at its cervical segment with consequent occlusion of the vessel in one patient while the other patient had 2 in the left renal and superior mesenteric arteries. The first was successfully treated with antibiotics, the second was managed by endovascular procedure and surgical repair.

Table 1 Clinical feature, CT findings and complications in 81 patients having left sided IE.

| Variable | N (% to 81) |
|--|-------------|
| <i>Underlying pathology</i> | |
| Rheumatic | 30 (37%) |
| Prosthetic valve | 21 (26%) |
| Normal heart | 19 (23.5%) |
| Congenital heart disease | 7 (8.6) |
| Degenerative valve disease | 4 (5%) |
| Mitral valve | 46 (56.8%) |
| Aortic valve | 19 (23.5%) |
| Both valves | 13 (16%) |
| Associated health problems | 25 (30.9) |
| <i>Organisms by blood culture & serology</i> | |
| Staph | 20 (24.7%) |
| Fungal | 8 (10%) |
| Strept | 14 (17.3%) |
| Brucella | 8 (10%) |
| Others | 16 (29.6%) |
| Culture/serology – negative | 15 (18.5%) |
| <i>Cerebral CTA findings</i> | |
| Normal | 30 (37%) |
| Cerebral embolization | 51 (63%) |
| Manifest embolization | 34 (42%) |
| Silent embolization | 17 (21%) |
| Silent infarction | 1 (1.2%) |
| Manifest infarction | 17 (21%) |
| Silent cerebral hemorrhage | 2 (2.5%) |
| Manifest cerebral hemorrhage | 20 (24.7%) |
| ICMA | 26 (32%) |
| <i>Major complications</i> | |
| Sepsis requiring ventilation or vasopressor | 23 (28.4) |
| Systemic embolization other than CNS | 49 (60.5%) |
| Heart failure | 40 (49.4%) |
| Death | 15 (18.5%) |

**Diagram 1** Cerebral CTA findings and prevalence of ICMA in both symptomatic and clinically silent groups.

Thirteen patients with ICMA were successfully treated by endovascular treatment (EVT). All procedures were performed under general anesthesia, 10 distal ICMA were treated with

PAO and 3 proximal ICMA were treated by coiling. There were no clinical changes after treatment in 11 patients. Transient complications occurred in two patients with distal ICMA in the form of a transient hemiparesis that resolved spontaneously within 48 h. Eight patients underwent cardiac surgery within 1 week of EVT without cerebral complications (Figs. 1–3).

The findings of cerebral CTA changed the treatment plans in 21 patients (25.6%). Eleven of them were neurologically asymptomatic and in 11 patients more than one change in the treatment plan was taken. These changes were as follows:

- Fifteen patients were referred for surgical or endovascular treatment of the ICMA based on the indications previously mentioned; 8 of them (53.3%) were asymptomatic. Thirteen patients were referred for endovascular treatment, 6 of them were neurologically silent. Two patients had postprocedure transient hemiparesis that resolved after 48 h. Two patients were referred for surgical treatment of ICMA that were not amenable to endovascular treatment; both were neurologically silent and had no procedure-related complications.
- Anticoagulation was stopped in 3 patients with prosthetic valve IE due to the presence of ICMA, 2 of them were silent.
- In 17 patients, we had to change the type of cardiac surgery from scheduled mechanical valve replacement to repair or biological valve replacement as they had ICMA or asymptomatic hemorrhage. Eight of them had no neurological manifestation.

Among the 26 patients with ICMA, 21 patients (81%) had their management strategy modified. This ratio was 73% in those with silent ICMA (11 out of 15 cases) where the detection of their asymptomatic ICMA led to the modification of their treatment plans. Mortality was 19.2% in patients with ICMA (5 out of 26) and was 66.7% in patients with ruptured ICMA (2 out of 3). The overall mortality incidence in this study was 15 patients (18.5%) and 12 of them (80%) had neurologic complications.

4. Discussion

In spite of the great advances in diagnostic and therapeutic modalities, infective endocarditis IE remains a challenging, non-tamed, wild disease with one of the highest rates of morbidity and mortality ever. In some studies, infective endocarditis mortality is classified as the fourth leading fatal infectious disease (19).

In most of the published reports and studies, there was a general agreement that every case outcome was significantly affected by the causative organism, the valve affected and the complications occurred to such a case (19). It is known that clinically manifested neurologic complications that are mostly due to acute brain embolization are evident in about 20–40% of endocarditis patients (20–23). Endocarditis neurologic sequelae are associated with poor outcomes (19).

The new surprising fact that was recently taken into consideration is the presence of large proportion of IE patients with brain embolization remained neurologically silent i.e. sub-clinical brain embolization (SCBE). This fact was proved either by autopsy data or by routine imaging. Computed tomography

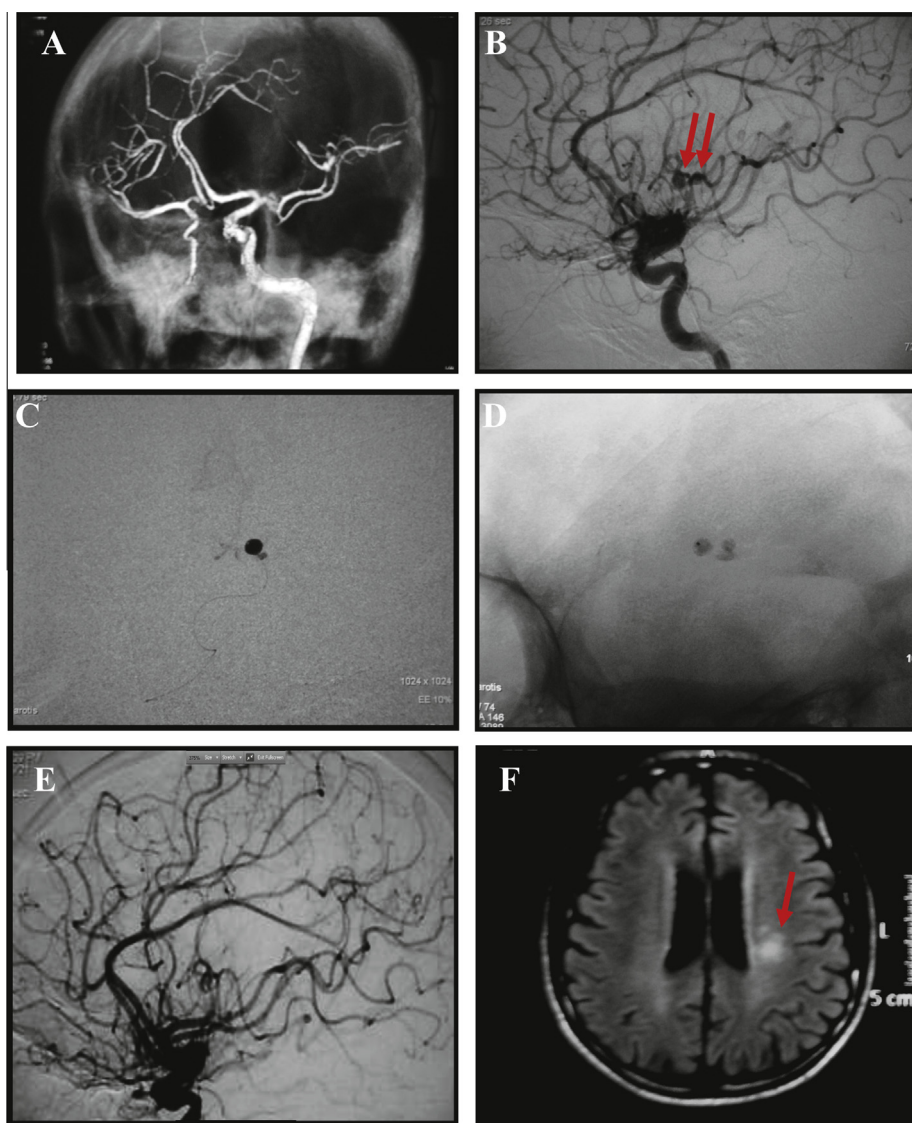


Fig. 1 (A) CTA in a clinically free patient showing Lt middle cerebral two distal mycotic aneurysms with occlusion of the Rt internal carotid artery in the neck. (B) Digital subtraction angiogram showing the two aneurysms- arrowed. (C) Microcatheter at the neck of the aneurysm. (D) Occlusion of both by Cyanoacrylate/Lipiodol mixture. (E) Digital subtraction angiogram after treatment. (F) MRI FLAIR post-treatment showing small clinically silent ischemic focus (arrowed).

was first tried in studies made by Thuny et al. and Di Salvo et al. (7,24,25).

Previous studies were inconsistent regarding the incidence of brain embolization in IE and did not use vascular imaging systemically. Thuny et al. (7) utilized cerebral and thoraco-abdominal CT that revealed silent emboli in only 8% of patients. Cooper et al. (6) performed brain MRI in 40 patients with IE and found acute brain embolization in 80% of patients. Iung et al. (26) performed routine cerebral MRI and detected ischemic lesions in 53.3% of their 64 patients. Iung et al. also performed routine abdominal and cerebral MRI in 58 patients with suspected IE within 7 days following admission. They modified therapeutic plans in 19% of their patients, based on cerebral MRI, including modification of surgical plans in 10% of patients (27).

MRI was found to be more sensitive than CT in evaluation of SCBE events. A fact that was made obviously clear in the

study made in Washington Hospital Center which revealed that SCBE events were as common as 48% of the studied population. It also stated that 95% of patients with Staph. endocarditis had MRI evidence of SCBE, despite only about their half had clinical manifestations (28).

The question about the impact of the SCBE posed on IE course and whether they can independently affect the outcome was addressed by same study from Washington Hospital Center showing that IE related mortality was equal between patients with clinical strokes and SCBE and it is much higher than in patients without brain embolization 56% versus 12% (28).

In the Finnish study that included 218 definite IE episodes found that neurologic complications are quite common in infective endocarditis and that it carries poor prognosis than neurologically uncomplicated cases. From the 218 cases studied, 84 (39%) had a neurologic complication and 58% of these

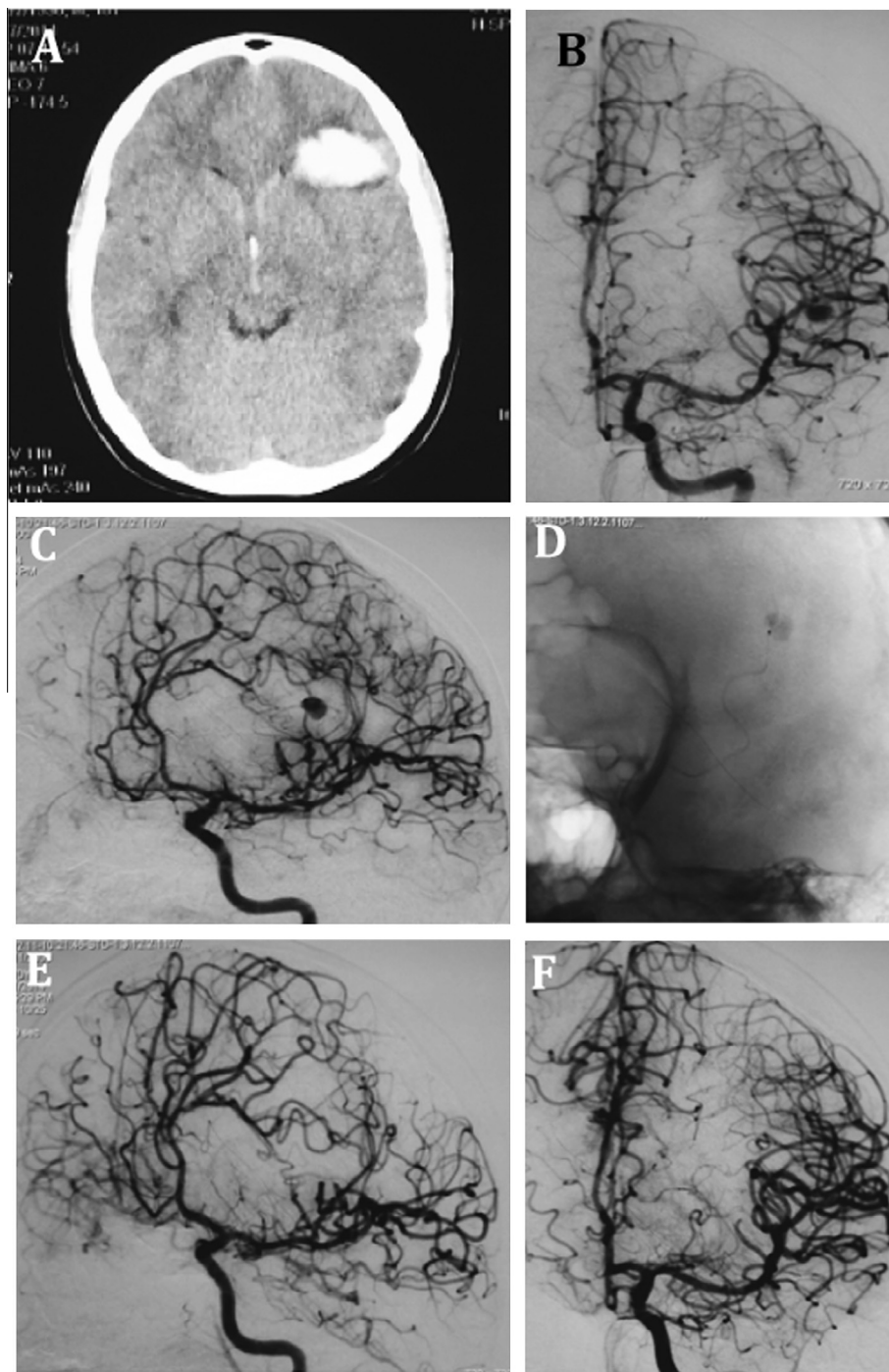


Fig. 2 (A) CT showing intracerebral and intraventricular bleeding secondary to rupture mycotic aneurysm. (B and C) Showing mycotic aneurysm along the left MCA branches. (D) Selective closure of the aneurysm and parent artery by Cyanoacrylate/Lipiodol mixture. (E and F) Final control showing closure of the aneurysm and MCA branch.

84 patients died. In contrast, the mortality rate was only 20% among those endocarditis patients without neurologic complications (29).

Most of the SCBE will cause ischemic insults or micro-hemorrhages that mostly remain clinically silent, but those causing ICMA are the biggest concern. Duval who examined 130 left sided infective endocarditis patients with MRI/MRA and

found that 16 patients (12%) had acute neurologic symptoms. Cerebral lesions were detected by MRI in 106 patients (82%), including ischemic lesions in 68 (64.1%) micro-hemorrhages in 74 (69.8%), and silent aneurysms in 10 (9.4%) (30).

In the French study by Thuny et al., 496 consecutive patients with definite IE were enrolled. Cerebral (CT) scan with contrast was systematically performed on admission in

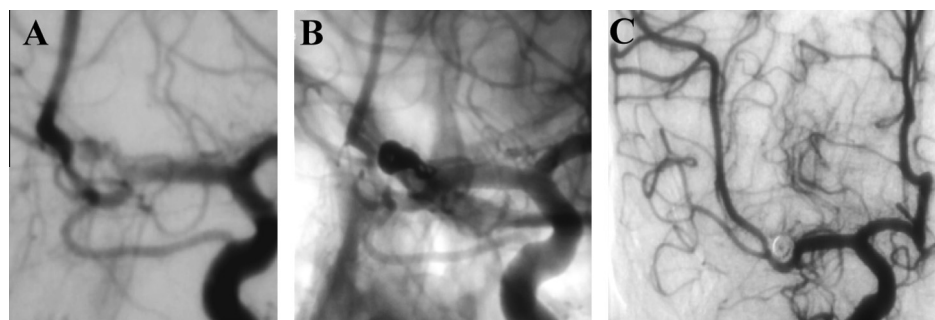


Fig. 3 (A) Ruptured mycotic aneurysm at the right MCA bifurcation with occlusion of the anterior temporal division. (B) Closure of the aneurysm by coiling. (C) Control angiogram showing total closure of the aneurysm with patent remaining MCA branches.

453 patients and was repeated if clinically indicated. A silent cerebral embolism was present in 17/453 patients (3.8%) (31).

In this study, we included 81 patients with left sided infective endocarditis. Neurologic complications were found in 51 patients (63%). All patients had cerebro-vascular imaging using CT angiography. The incidence of neurologic complications in this study is higher than in the literature, it ranges between 20% and 40% in most of the published reports (17,21–23). This can be due to the detection of silent cases by CTA screening done and the fact that we work in a tertiary care center and receive complicated patients from other centers late in their course.

Considering ICMA from the other than CNS complications, the results derived from this study were comparable with the results were derived from Washington Hospital Center study (28), Duval et al. study (30), and Thuny et al. study (31). Clinically manifesting ICMA incidence was 13.6% (11 among the 81 studied patients). The clinical presentation in these cases was ischemic stroke and was complicated in 7 of them by hemorrhagic transformation. By routine screening this incidence jumped to be 32.1% (15 more silent ICMA cases). This means that silent ICMA comprised 57.7% (15 out of 26) from all ICMA cases, which is relatively a large ratio.

Regarding IE related mortality, the overall mortality incidence in this study was significantly low (18.5%) compared to the known IE related mortality which ranges from 26 to more than 31% (32,33). This study confirms the fact that CNS complications carry higher mortality rates than neurologically free patients. Among the mortality cases that occurred in this study 80% (12 out of 15) had neurologic complications. Re-reading this data from the other view made mortality incidence 14.8% vs. 3.7% in patients with vs. without CNS complications respectively.

In this study routine cerebrovascular imaging had caused a remarkable decline in endocarditis related mortality in patients with neurologic complications 14.8% (12 of 81 patients) compared to the universal reports, where the mortality in equivalent population in the Finnish study (58%) (30), the Washington university hospital study (62%) (28) or in Sonnevile, Mirabel, et al. study (62%) (34). Despite that we had a higher incidence of neurologic involvement in our patients, this decline in mortality rates is a strong proof that early detection and the sound optimization of management plans in patients found to have any acute brain embolization whether manifesting or silent can dramatically affect mortality rates.

ICMA cases in the past were only discovered when symptomatic and remain silent until massive complications occur, in most of the cases massive intracranial hemorrhage. The literature reports mortality rates around 60% and higher in endocarditis patients with ICMA. This rate jumps abruptly to become 80–90% if ICMA ruptures (35,36). However by routine cerebral CTA, and by the strategy we adopted targeting early detection of silent mycotic aneurysms, and appropriate sound management of aneurysms needing intervention either by endovascular repair or by surgical clipping, mortality was reduced to 15.3% (4 out of 26). This ratio (15.3%) counts for total ICMA cases mortality which is around the fourth of the rates in published reports (60%) (5). The mortality rate among patients with ruptured ICMA was 66.7% (2 out of 3) which is comparable with the published data 80–90%.

The cost effectiveness of routine screening appeared to be very favorable by early detection and appropriate treatment plan and modification of the affected cases. Comparing the cost of routine cerebral CTA in patients with definite left sided IE to the lives saved (reducing mortality from 60% to 15.3%) added to the costs that might have been spent for management of patients if they develop unexpected massive intracranial hemorrhages from silent ICMA ruptures (such as having neurosurgical intervention or special care to comatosed patients), all these come in favor of routine CTA imaging to all patients. It is worth mentioning that none of the patients who went for neurovascular procedure had related permanent morbidity or mortality. To our knowledge this is the first study to use routine cerebral CTA to assess brain embolization in patients with left-sided IE and its impact on the treatment plans.

5. Conclusion

Routine assessment of patients with aortic/mitral infective endocarditis (IE) by cerebral CTA changed the treatment plans in a large group of patients with significant reduction in the mortality rate. This screening method is safe and may potentially improve the outcome of IE patients. We recommend more studies to compare the implementation of routine screening by cerebral CTA versus the standard care in IE patients.

Conflict of interest

None declared.

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